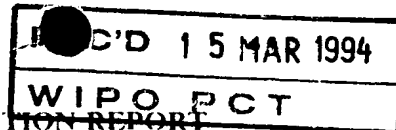


## PATENT COOPERATION TREATY

PCT



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>MBUS 1129</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/GB 92/02334</b>	International filing date (day/month/year) <b>16/12/1992</b>	Priority date (day/month/year) <b>16/12/1991</b>
International Patent Classification (IPC) or national classification and IPC <b>C07D257/02</b>		
Applicant <b>JOHNSON MATTHEY PUBLIC LIMITED COMPANY et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 9 sheets.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings amended during international preliminary examination and/or containing rectifications made before this Authority.

These annexes consists of a total of 53 sheets.

3. This report contains indications and corresponding pages relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand <b>08/07/1993</b>	Date of completion of this report <b>11. 03. 94</b>
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer  <b>LA. Feller</b>

## I. Basis of the report

1. This report has been drawn up on the basis of:

☐ the international application as originally filed.

☒ the description, pages \_\_\_\_\_, as originally filed,  
pages \_\_\_\_\_, filed with the demand,  
pages 1-45 \_\_\_\_\_, filed with the letter of 15/12/93,  
pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_,

☒ the claims, No. \_\_\_\_\_, as originally filed,  
No. \_\_\_\_\_, as amended under Article 19,  
No. \_\_\_\_\_, filed with the demand,  
No. 1-45 \_\_\_\_\_, filed with the letter of 15/12/93,  
No. \_\_\_\_\_, filed with the letter of \_\_\_\_\_,

☐ the drawings, sheets/fig \_\_\_\_\_, as originally filed,  
sheets/fig \_\_\_\_\_, filed with the demand,  
sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

2. The amendments have resulted in the cancellation of: pages: \_\_\_\_\_  
sheets of drawings/figures No.: \_\_\_\_\_.

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed:

In Claim 1 and 19 a disclaimer ("other than quinoline") has been inserted. It appears that this has not been effected in view of novelty destroying documents but to exclude matter which cannot be considered to be inventive. It has to be stressed that disclaimers are not allowable in order to fulfil the inventive step requirement.

The description contains on page 6, lines 1 and 2 "and there are preferably 3 or 4 nitrogen atoms" which has no original disclosure as it appears.

## 4. Additional observations, if necessary:

With the exception of the matter indicated above the Claims are based on the application as originally filed:

Claim 1: Original Claim 1 in combination with original Claims 1, 2 and 7; page 4, lines 25, 26, 21; page 5, lines 1, 2

Claim 2: Original Claim 4

Claim 3: Original Claim 6

Claims 4-18: Original Claims 8-17, 20-23, 26

Claims 19-41: Original Claims 27, 28, 33-42, 44-46, 49-52, 55-58

Claims 42-45: Original Claims 59-62.

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/GB92/02334

—!!—!!—!!—!!—!!—!!—

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

---

## 1. STATEMENT

Novelty (N)	Claims 1-45, yes _____	YES
	Claims _____	NO
Inventive Step (IS)	Claims 8, 14, 15, 29, 34, 35, yes _____	YES
	Claims 1-7, 9-13, 16-28, 30-33, 36-45, no _____	NO
Industrial Applicability (IA)	Claims 1-45, yes _____	YES
	Claims _____	NO

---

## 2. CITATIONS AND EXPLANATIONS

## 1. Cited documents

EP-A-0296522= D1  
EP-A-0305320= D2  
WO-A-9105762= D3  
EP-A-0434385= D4  
WO-A-9216494= D5

The indicated designation is used throughout the examination procedure.

## 2. Novelty

The subject matter of the Claims differs from that of the cited prior art D1-D3 in that it refers to compounds comprising two cyclic polyamines linked together, not foreseen in D1-D3. The difference between the subject matter as claimed and D4 resides in the fact that the link comprises an aromatic or heteroaromatic moiety not specifically considered in D4.

---

Since the priority documents are not available at the moment it could not be checked whether the claimed priority date 16/12/91 is justifiable. On the condition that it is acceptable D5 can remain outside consideration at this stage, but will be highly relevant in the possible regional phase. Subject matter as claimed can be considered to be novel in respect of D1-D4.

It would appear that the disclaimer of Claim 19, lines 18 and 19 refer to the literature indicated on page 6 of the application.

### 3. Inventive step - broadness of the claims

#### 3.1 Subjective problem

According to the application (see page 1) the problem underlying the application is the provision of compounds having activity against infection by HIV.

#### 3.2 Closest prior art

The closest prior art is D4 since the subject matter of your claims is comprised by Claim 1 of D4 (selection) and the compounds of D4 have qualitatively the same pharmacological activity.

#### 3.3 Problem which has been objectively solved

In view of the information and data given in the description page 43-49 the tested compounds obviously solve the technical problem defined above.

#### 3.4 Evaluation of the solution of the problem

For the subject matter of the claims D4 is the closest prior art (see above). With these products the problem to provide further compounds which are active against HIV is also solved.

From this document, the person skilled in the art searching for a solution to the problem defined above would have considered further variation of the "link".

It has also to be stressed that e.g.  $-(CH_2)_3-$  and phenylene can be considered as equivalent spacer groups (see e.g. Essentials of Medicinal Chemistry (Wiley), second edition 1988,

page 82).

3.5 In spite of the opinion indicated above the presence of an inventive step for specific subject matter could be acknowledged if it is made credible by test results that apart from the problem defined above another more exacting problem, which can be deduced from the original application (e.g. surprising improvements), has actually been solved by using originally disclosed technical characteristics which should be incorporated in claim 1.

It should be taken into consideration that only the structurally closest compounds of the closest prior art D4 are useful for a meaningful comparison. The application contains already comparative data with AZT but since AZT is not the closest prior art the data are prima facie not relevant for inventive step considerations. On the other hand D4 also contains comparative data with AZT. Since the test procedure is actually the same in D4 and the application the data of D4 and the application could be compared. The closest prior art compound is 1,1'-(1,5-pentanediy1) bis-1,4,8,11-tetraazacyclotetradecane of D4 to be compared with compound B of the application. For this prior art compound no data are available from D4; the corresponding value should therefore be provided by the Applicant and be compared to the compounds of the application wherein A is phenylene and its equivalents (pyridinediy1, thiophenediy1).

The ED<sub>50</sub> value for the corresponding 1,6-hexanediy1 compound of D4 (compound H) is 0.54 for HIV-1 (see table of D4, pages 4/5 ) and could be taken for a comparison with the compounds which are structurally compareably (see compound J, K and L). Since those compounds compare favourably an inventive step could therefore be acknowledged for subject matter of Claims 8, 14, 15, 29, 34 and 35.

### 3.6 Breadth of the claims

The breadth should be such that it could be expected that the compounds comprised would actually solve the problem underlying the invention defined in point 3.5. It is noted that the Applicant has deleted compounds H, I, S, U and V showing

an unfavourable level of activity. It is also apparent that the activity depends also on the kind of link (see compound V). It is considered not to be acceptable that specific possibilities which do not solve the problem are disclaimed; a positiv formulation should be chosen. The definition of A must be such that all possibilities comprised could be expected to solve the problem on which an inventive step could be based. Specifically all features which are essential to solve that problem should go into Claim 1.

#### 4). Industrial applicability

As far as the compounds comprised by the claims of the application can be prepared and have some useful property no objection arises.

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/GB92/02334

## VI. Certain documents cited

### 1. Certain published documents

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
-------------------------------	--------------------------------------	---------------------------------	---

WO-A-9216494	01/10/92	11/03/92	15/03/91
--------------	----------	----------	----------

### 2. Non-written disclosures

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)
--------------------------------	--	---



## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

## 1. Clarity of the claims, support by the description

- a) The general expression "aromatic or heteroaromatic moiety", which is contained in Claim 1 and 19 should be defined according to the description.
- b) In Claim 1 formula (I) R and R' should be replaced by  $\text{CH}_2$ .

## 2). Description

The description should be amended according to the claims.

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>MBUS 1129</b>	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/GB 92/ 02334</b>	International filing date (day/month/year) <b>16/12/1992</b>	Priority date (day/month/year) <b>16/12/1991</b>
International Patent Classification (IPC) or national classification and IPC <b>C07D257/02</b>		
Applicant <b>JOHNSON MATTHEY PUBLIC LIMITED COMPANY et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


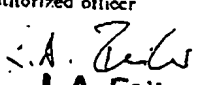
2. This REPORT consists of a total of 9 sheets.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings amended during international preliminary examination and/or containing rectifications made before this Authority.

These annexes consists of a total of 53 sheets.

3. This report contains indications and corresponding pages relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand <b>08/07/1993</b>	Date of completion of this report <b>11. 03. 94</b>
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel: (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer  <b>LA. Feller</b>

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/GB92/02334

I. Basis of the report

1. This report has been drawn up on the basis of:

☐ the international application as originally filed.

☒ the description, pages \_\_\_\_\_, as originally filed,  
pages \_\_\_\_\_, filed with the demand,  
pages 1-45 \_\_\_\_\_, filed with the letter of 15/12/93,  
pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_,

☒ the claims, No. \_\_\_\_\_, as originally filed,  
No. \_\_\_\_\_, as amended under Article 19,  
No. \_\_\_\_\_, filed with the demand,  
No. 1-45 \_\_\_\_\_, filed with the letter of 15/12/93,  
No. \_\_\_\_\_, filed with the letter of \_\_\_\_\_,

☐ the drawings, sheets/fig \_\_\_\_\_, as originally filed,  
sheets/fig \_\_\_\_\_, filed with the demand,  
sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

2. The amendments have resulted in the cancellation of: pages: \_\_\_\_\_  
sheets of drawings/figures No.: \_\_\_\_\_.

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed:

In Claim 1 and 19 a disclaimer ("other than quinoline") has been inserted. It appears that this has not been effected in view of novelty destroying documents but to exclude matter which cannot be considered to be inventive. It has to be stressed that disclaimers are not allowable in order to fulfil the inventive step requirement.

The description contains on page 6, lines 1 and 2 "and there are preferably 3 or 4 nitrogen atoms" which has no original disclosure as it appears.

4. Additional observations, if necessary:

With the exception of the matter indicated above the Claims  
are based on the application as originally filed:

Claim 1: Original Claim 1 in combination with original Claims  
1, 2 and 7; page 4, lines 25, 26, 21; page 5, lines 1, 2

Claim 2: Original Claim 4

Claim 3: Original Claim 6

Claims 4-18: Original Claims 8-17, 20-23, 26

Claims 19-41: Original Claims 27, 28, 33-42, 44-46, 49-52,  
55-58

Claims 42-45: Original Claims 59-62.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/GB92/02334

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-45, yes	YES
	Claims	NO
Inventive Step (IS)	Claims 8, 14, 15, 29, 34, 35, yes	YES
	Claims 1-7, 9-13, 16-28, 30-33, 36-45, no	NO
Industrial Applicability (IA)	Claims 1-45, yes	YES
	Claims	NO

2. CITATIONS AND EXPLANATIONS

1. Cited documents

EP-A-0296522= D1  
EP-A-0305320= D2  
WO-A-9105762= D3  
EP-A-0434385= D4  
WO-A-9216494= D5

The indicated designation is used throughout the examination procedure.

2. Novelty

The subject matter of the Claims differs from that of the cited prior art D1-D3 in that it refers to compounds comprising two cyclic polyamines linked together, not foreseen in D1-D3. The difference between the subject matter as claimed and D4 resides in the fact that the link comprises an aromatic or heteroaromatic moiety not specifically considered in D4.

Since the priority documents are not available at the moment it could not be checked whether the claimed priority date 16/12/91 is justifiable. On the condition that it is acceptable D5 can remain outside consideration at this stage, but will be highly relevant in the possible regional phase. Subject matter as claimed can be considered to be novel in respect of D1-D4.

It would appear that the disclaimer of Claim 19, lines 18 and 19 refer to the literature indicated on page 6 of the application.

### 3. Inventive step - broadness of the claims

#### 3.1 Subjective problem

According to the application (see page 1) the problem underlying the application is the provision of compounds having activity against infection by HIV.

#### 3.2 Closest prior art

The closest prior art is D4 since the subject matter of your claims is comprised by Claim 1 of D4 (selection) and the compounds of D4 have qualitatively the same pharmacological activity.

#### 3.3 Problem which has been objectively solved

In view of the information and data given in the description page 43-49 the tested compounds obviously solve the technical problem defined above.

#### 3.4 Evaluation of the solution of the problem

For the subject matter of the claims D4 is the closest prior art (see above). With these products the problem to provide further compounds which are active against HIV is also solved.

From this document, the person skilled in the art searching for a solution to the problem defined above would have considered further variation of the "link".

It has also to be stressed that e.g.  $-(CH_2)_3-$  and phenylene can be considered as equivalent spacer groups (see e.g. Essentials of Medicinal Chemistry (Wiley), second edition 1988,

page 82).

3.5 In spite of the opinion indicated above the presence of an inventive step for specific subject matter could be acknowledged if it is made credible by test results that apart from the problem defined above another more exacting problem, which can be deduced from the original application (e.g. surprising improvements), has actually been solved by using originally disclosed technical characteristics which should be incorporated in claim 1.

It should be taken into consideration that only the structurally closest compounds of the closest prior art D4 are useful for a meaningful comparison. The application contains already comparative data with AZT but since AZT is not the closest prior art the data are prima facie not relevant for inventive step considerations. On the other hand D4 also contains comparative data with AZT. Since the test procedure is actually the same in D4 and the application the data of D4 and the application could be compared. The closest prior art compound is 1,1'-(1,5-pentanediy1) bis-1,4,8,11-tetraazacyclotetradecane of D4 to be compared with compound B of the application. For this prior art compound no data are available from D4; the corresponding value should therefore be provided by the Applicant and be compared to the compounds of the application wherein A is phenylene and its equivalents (pyridinediy1, thiophenediy1).

The ED<sub>50</sub> value for the corresponding 1,6-hexanediyl compound of D4 (compound H) is 0.54 for HIV-1 (see table of D4, pages 4/5) and could be taken for a comparison with the compounds which are structurally compareably (see compound J, K and L). Since those compounds compare favourably an inventive step could therefore be acknowledged for subject matter of Claims 8, 14, 15, 29, 34 and 35.

### 3.6 Broadness of the claims

The breadth should be such that it could be expected that the compounds comprised would actually solve the problem underlying the invention defined in point 3.5. It is noted that the Applicant has deleted compounds H, I, S, U and V showing

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/GB92/02334

an unfavourable level of activity. It is also apparent that the activity depends also on the kind of link (see compound V). It is considered not to be acceptable that specific possibilities which do not solve the problem are disclaimed; a positive formulation should be chosen. The definition of A must be such that all possibilities comprised could be expected to solve the problem on which an inventive step could be based. Specifically all features which are essential to solve that problem should go into Claim 1.

4). Industrial applicability

As far as the compounds comprised by the claims of the application can be prepared and have some useful property no objection arises.



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/GB92/02334

## VI. Certain documents cited

### 1. Certain published documents

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO-A-9216494	01/10/92	11/03/92	15/03/91

### 2. Non-written disclosures

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

## 1. Clarity of the claims, support by the description

- a) The general expression "aromatic or heteroaromatic moiety", which is contained in Claim 1 and 19 should be defined according to the description.
- b) In Claim 1 formula (I) R and R' should be replaced by  $\text{CH}_2$ .

## 2). Description

The description should be amended according to the claims.